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ON THE METHODOLOGY OF STUDYING AGING IN HUMANS

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1. Introduction

Methods for studying the aging of human beings cover a wide span of scientific endeavor. The literature in the field is large and research is expanding rapidly. Some indication of the scope of research activity on aging is obtained from the following listing of topics found in the 15-page table of contents of Nathan Shock's bibliography of gerontology [39].

(A) Biology of aging (1) cellular biology and physiology, (2) climate and geography, (3) exercise, (4) longevity (comparative physiology, diet, drugs, heredity, marriage, mortality rates, national groups, occupation, sex), (5) metabolism, (6) mortality rates, (7) nutrition, (8) parental age, (9) physiological age, (10) rejuvenation,

(B) Organ systems,

(C) Geriatrics,

(D) Psychological processes,

(E) Social and economic aspects.

Out of this maze of information and theory a number of lines of thought have been gathered in this paper to focus attention on some biostatistical phases of the enigma of aging. That this is a subject which is eminently biostatistical is obvious from its nature. Observation and experimentation are carried out all the way from the most basic cellular level up through drosophila, flatworms, rotifers, rats, horses, elephants and man. As one proceeds up the developmental ladder experimentation is replaced by observation and direct knowledge is replaced by indirect inference. At the human level our real understanding of aging is indeed poor, depending as it must on the evidence of vital statistics and hampered by the time required to follow groups of subjects through an appreciable part of their lifetime. A difficulty, not reserved for the problem of aging but particularly nasty in this case, is the lack of specifiability of conditions under which observations are made. Statistically speaking, nature is rather poor at the design of experiments, especially when it comes to untangling the effects on human mortality of environment and heredity, of endogenous and exogenous factors, and of exposure and susceptibility.

2. Some results from animal experiments

Before discussing specific methodology we turn to a few results from work done on animals, fish, and insects. Some remarkable findings have to do with nutrition. When immature rats are fed a normal, balanced diet which, however, is low in calories, their life span is increased greatly over that of well-fed controls [25]. Reduced diet slows growth, and rats can be maintained in an immature state up to about 1000 days and still show growth upon increasing the diet. Analogously, restricting the food of the water flea and of ticks prolongs life [6]. (Note: for convenience some references will be made to review publications from which detailed references can be obtained.) In some generality it can be said that undernourishment before maturity delays maturity and prolongs life. (There are exceptions, of course.) Undernourishment in mature individuals seems to have little beneficial effect but overnourishment and subsequent obesity apparently shorten life.

A related set of findings has to do with temperature. At low temperatures insects, fish, and frogs survive longer than at higher ones [6]. The differences are large, amounting to a doubling of the lifetime of some fish and a vast increase in the life of insects. Elevation of temperature is found to increase the heart rate and hence the metabolic rate. This acceleration is associated with very nearly proportionate decrease in duration of life. Animals, such as "bats with poor thermo-regulation and a normally low rate of metabolism are precisely those whose life span is far longer than that of other mammals of similar size. Inversely to bats, shrews with their very high metabolic rate and fecundity are among the shortest lived mammals." (Quoted from Bourlière [2].)

From the work on nutrition, temperature, and metabolic rate there has grown the notion that the slower the "rate of living" the longer the life span. It has been stated that individuals are born with a certain amount of vitality which may be expended in different ways at different rates [34]. How an individual spends his early life is presumed to have far reaching effect on his life span. Early illness experience leaves permanent scars to which are added increments of damage corresponding to each "insult" which occurs during a lifetime. Smoking, overeating, hard labor, and so forth, act as accelerators, speeding up the rate of living and hence decreasing length of life. See [17], page 344.

In addition to the temperature and nutrition research a rapidly developing field of inquiry has developed in studying radiation effects among animals. Upton [44] summarizes his review paper by stating, "The life span is shortened by exposure to ionizing radiation in proportion to the amount of radiation absorbed." Alexander [1] states, "A long-term effect which follows exposure to ionizing radiation is a decrease in life span. The carcinogenic action of these radiations can only explain a very small part of the increased rate in mortality. The general pattern of death in an irradiated group can best be described as an accelerated aging." Here we have, if the above is true, an auxiliary tool to use in studying aging. We can induce radiation aging in various ways to get leads on the aging of humans.

3. Force of mortality

Up to this point no mention has been made of a definition of aging and in this paper no sophisticated definition will be attempted. We will merely consider as the object of study a measure of aging called variously "risk of death" or "force of mortality." As we shall see, this measure is a kind of endpoint quantity. It ignores physical vigor, learning ability, and a host of other indices which have been used in aging research. It cannot be determined for an individual; it is a measure associated with a population. Notions such as force of mortality, probability of death, and death rate are the stock in trade of vital statisticians and actuaries. Some recent authors have shown confusion about these ideas, however, and a brief explanation seems to be in order. We begin by using life table notions. Consider for the moment only age changes, ignoring environmental changes occurring with the passing of time. Let l_x be the usual life table function representing the survivors to age x of l_0 people who come under observation at birth. The force of mortality μ_x at age x is defined as the negative relative rate of change of l_x,

$$\mu_x = -\frac{1}{l_x}\frac{dl_x}{dx}. \tag{1}$$

It can be interpreted as an "instantaneous death rate." The quantity $\mu_x dx$ is the conditional probability of a person dying in age interval x, $x + dx$ given dx is small and the person has already survived to age x. The force of mortality μ_x is one of the fundamental indices of mortality and is a pertinent quantity of study.

The probability of a person dying between age x and $x + n$ given he is alive at age x can be written as

$$({}_nq_x) = 1 - \exp\left(-\int_x^{x+n} \mu_s ds\right). \tag{2}$$

Denote the mean force of mortality from age x to $x + n$ by $({}_n\bar{\mu}_x)$,

$$({}_n\bar{\mu}_x) = \frac{1}{n}\int_x^{x+n} \mu_s ds = \frac{1}{n}\int_x^{x+n} -\frac{1}{l_s}\left(\frac{dl_s}{ds}\right)ds \approx \frac{-1}{nl_{x+n/2}}(l_{x+n} - l_x) = \frac{({}_nd_x)}{nl_{x+n/2}}, \tag{3}$$

where $({}_nd_x)$ is the number of deaths between age x and $x + n$. We now see the analogy with the ordinary death rate $({}_nm_x)$. Replace $({}_nd_x)$ by $({}_nD_x)$, the number of observed deaths between ages x and $x + n$ during a time period of T years. Replace $nl_{x+n/2}$ by $({}_nP_x)T$, the number of person-years lived between ages x and $x + n$ during the observation period, $({}_nP_x)$ being the population between age x and $x + n$ at midperiod. Then we can write

$$({}_nm_x) = \frac{({}_nD_x)}{({}_nP_x)T} \approx ({}_n\bar{\mu}_x). \tag{4}$$

One should note that the death rate is not a probability; it is an estimate of the mean force of mortality between ages x and $x + n$.

4. Description and prediction of death rates

The relation of death rate to age has been extensively studied for over 100 years. As an illustration recent death rates for the United States are presented in figure 1. Plotted on semilog paper in figure 2 are rates for the United States and Sweden for 1955. We note the approach to linearity at the older ages in the latter figure.

In 1825 Gompertz published his famous paper [12] in which he described the relation of force of mortality and age as an exponential function, which can be written as

$$\mu_x = e^{B+Cx} = \beta c^x. \tag{5}$$

He had observed that this appeared to fit mortality data, especially at the older ages. Later Makeham [23] generalized this somewhat to obtain the Makeham-Gompertz law of mortality,

$$\mu_x = \alpha + \beta c^x. \tag{6}$$

The effect of α is to make the function fit better the mortality data for younger ages, but not ages under 10. Here α was inserted in the formula to attempt to account for environmental risks. These seemed most important (relatively) at the younger ages and the effect of α is most noticeable there. Its value in practice does not always seem sensible, however, and many writers appear to discount its biological significance (Greenwood [15]). Out of curiosity, the author made a rough fit of this function to United States data. The fit was not exceptional, differing from observed rates at both low and high ages. The fits obtained, however, were quite reasonable for Sweden, England and Wales and a number of other countries. At ages above 50 years, where the log death rates appear to be linear, the simpler Gompertz curve fits closely.

While on this subject of the Makeham-Gompertz function, it should be noted that one of the most elegant papers on the application of this function to human data was published in 1934 by Cramér and Wold [7]. They took Swedish mortality data from 1801 to 1930 at ages from 30 to 90. For each 5 year calendar period, 1801–1805, 1806–1810, $\cdots$, they fitted the Makeham-Gompertz curve to 5 year age specific death rates. Each fitting provided estimates of the parameters α, β, and $\log c$ for each of the five year calendar periods. These parameters were then separately fitted by curves empirically chosen to aid in interpolation and extrapolation. For instance, the estimates of $\log c$ as obtained for each 5 year period were fitted by a logistic function. From the security of hindsight the author recently examined the forecast of mortality for Swedish males in 1952 which was made by Cramér and Wold in the early 1930's, see figure 3. It was not very accurate but the shape of the curve was closely analogous to the observed one. They missed their forecast primarily because of the recent precipitous drop in

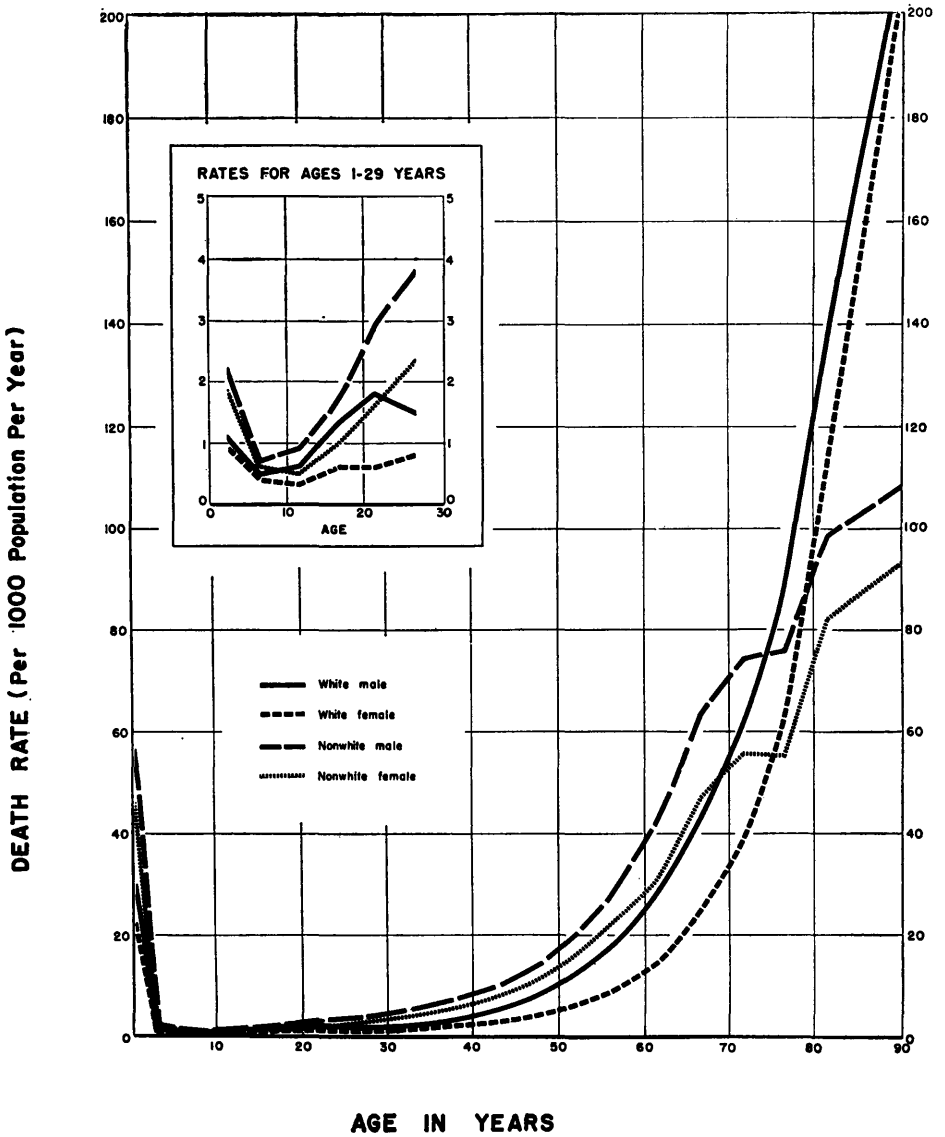

FIGURE 1

Death rates by age, color, and sex: United States, 1957, (see reference [32]).

mortality at ages under 50. In 1930 this drop was already underway but it had been obscured by the high death rates of the years 1916–1920. By deleting the influenza pandemic of 1918 their forecast might have been improved considerably.

There are obvious objections to restricting the study of mortality to the death

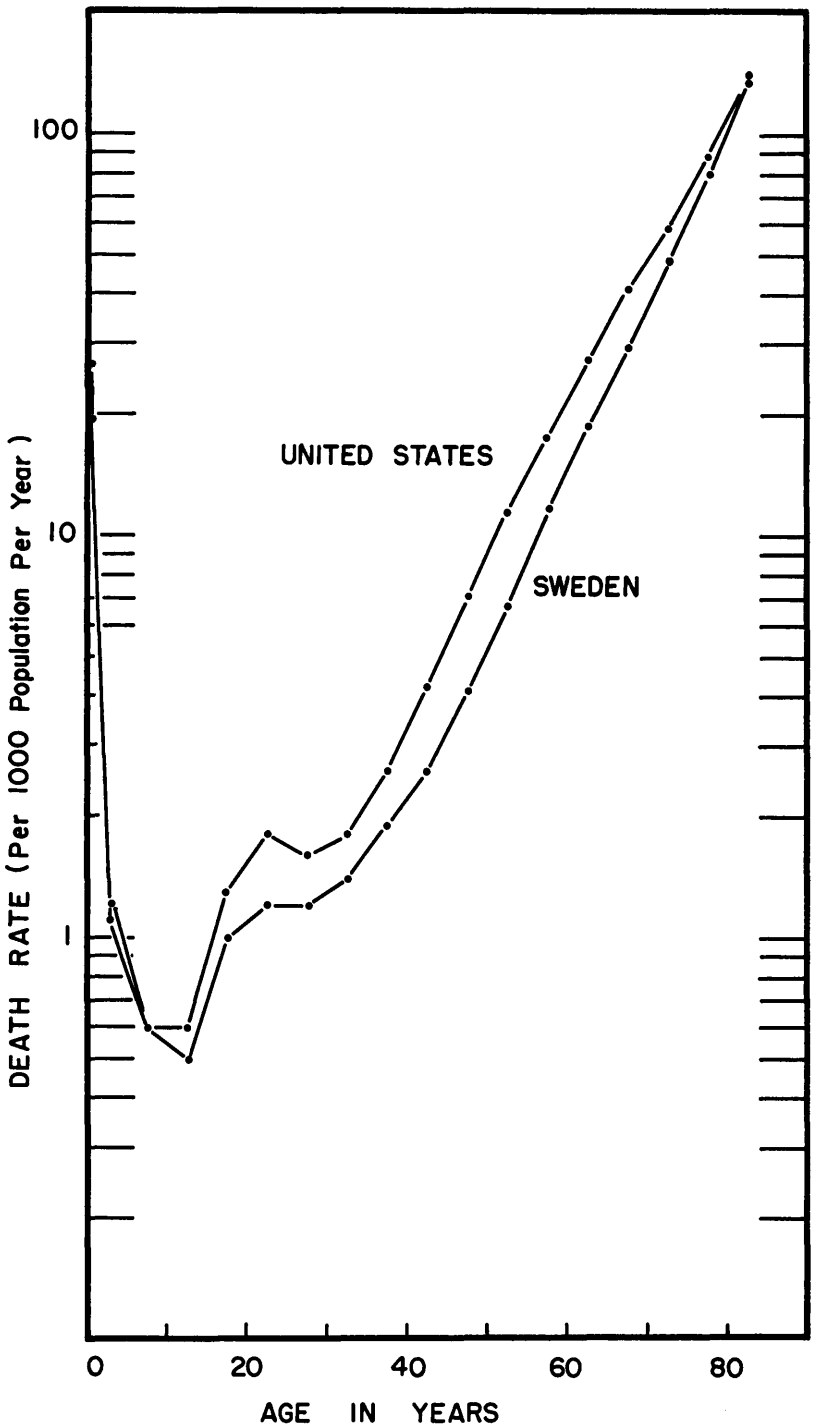

FIGURE 2

Death rates by age: white males, United States; males, Sweden; 1955, (see reference [45]).

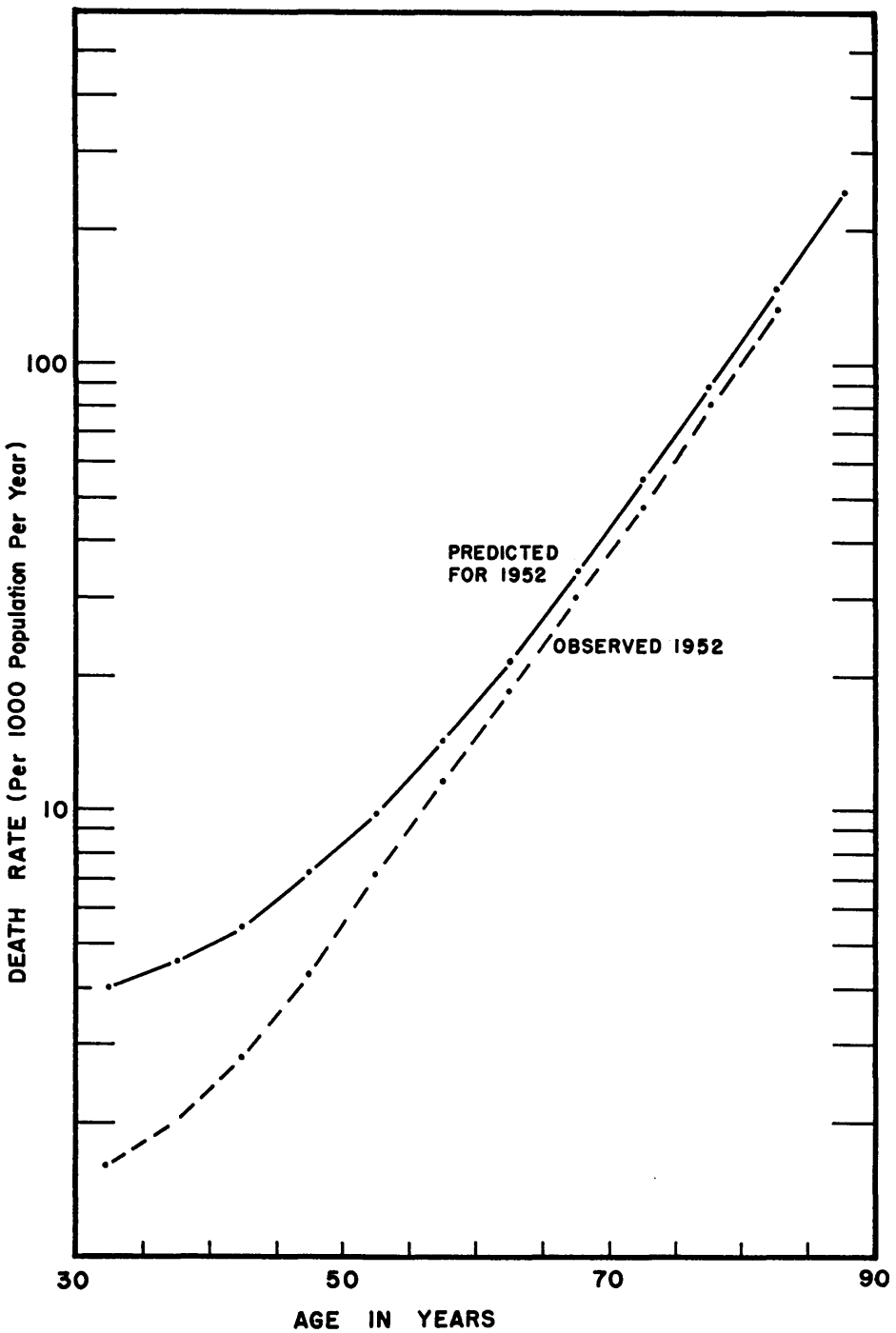

FIGURE 3

Death rates by age: Swedish males, 1952,
predicted by Cramér and Wold in 1934 and observed in 1952,
(see references [7], [43]).

rates based on a fixed period of time. At each successive age a different group of people is involved, each group having experienced different health hazards. Consequently much effort has gone into studying cohorts of people as they progress through life. Cramér and Wold did this for each five year cohort from those born about 1770 to those born about 1840. Makeham-Gompertz curves fit fairly well the age specific death rates of these cohorts. The parameters α, β, and $\log c$ were estimated for each cohort and extrapolated. This provided additional forecasts of 1952 death rates which turned out to be somewhat closer to the actual ones than obtained in the work just described.

5. Methods for studying aging

Many methods for studying aging in human beings are suggested by the animal experiments and the relation between age and force of mortality which have been discussed above. In this paper attention is directed to the effects of environment with particular emphasis on possible permanent effects of stress suffered early in life.There is little doubt, for example, that whole body irradiation early in life (the acute effects of which disappear after a time), causes lasting damage. This damage is reflected in the mortality curve as a displacement upwards from the mortality curve for unirradiated controls [38]. The mortality curves have an appearance corresponding to a sudden aging in the irradiated subjects. Opposed to these results is the finding [8], [41] that some stresses other than radiation, such as large challenge doses of typhoid vaccine, nitrogen mustard, or brief thermal shocks, do not lead to increases in observed death rates of survivors over those of controls.

What is the story with human beings? What methods might be used to investigate this problem? The type of results desired are those obtainable from experiment rather than from observation. If we could perform them, such experiments would involve random selection of human subjects, appropriate assignment of stresses early in life, and then continuous follow-up throughout life. Even with the use of animals such experiments are far from common partly due to the time required. Considering the impossibility of direct experimentation on humans, we set as a goal the approximation to such experimentation through the indirect, observational methods available to us. A number of approaches to this goal will be considered in the remainder of this paper. Some methods are very indirect indeed but even these may contribute some bits of information.

5.1. *Mortality curve analysis.* As mentioned above, mortality data have been under intensive scrutiny for over 100 years. A few studies which seem particularly pertinent will be considered here. From the general viewpoint, that is from the viewpoint of the total death rate, what sorts of information can be obtained? In the early 1930's Kermack, McKendrick, and McKinlay [19] were struck by certain regularities in the age specific death rates of England and Wales. (See [14] for comment.) They assumed that the force of mortality was in a steady state with respect to time up to 1845 and consequently they used the 1845 data

as a standard. Rates for later years were expressed as percentages of the 1845 rates at the corresponding ages. They observed an amazing regularity among the cohorts. Within each diagonal of the table the rates were all nearly the same percentages of the 1845 rates. It was as if improvement in health began at the early ages and was progressively delayed at older ages. It was also as if once a cohort got off to a good start it stayed relatively "younger" throughout its lifetime with the same proportional improvement age by age over the initial steady state. The mortality curve for such a "younger" population would be displaced downward and parallel to the older curve as shown in the heavy lines in figure 4.

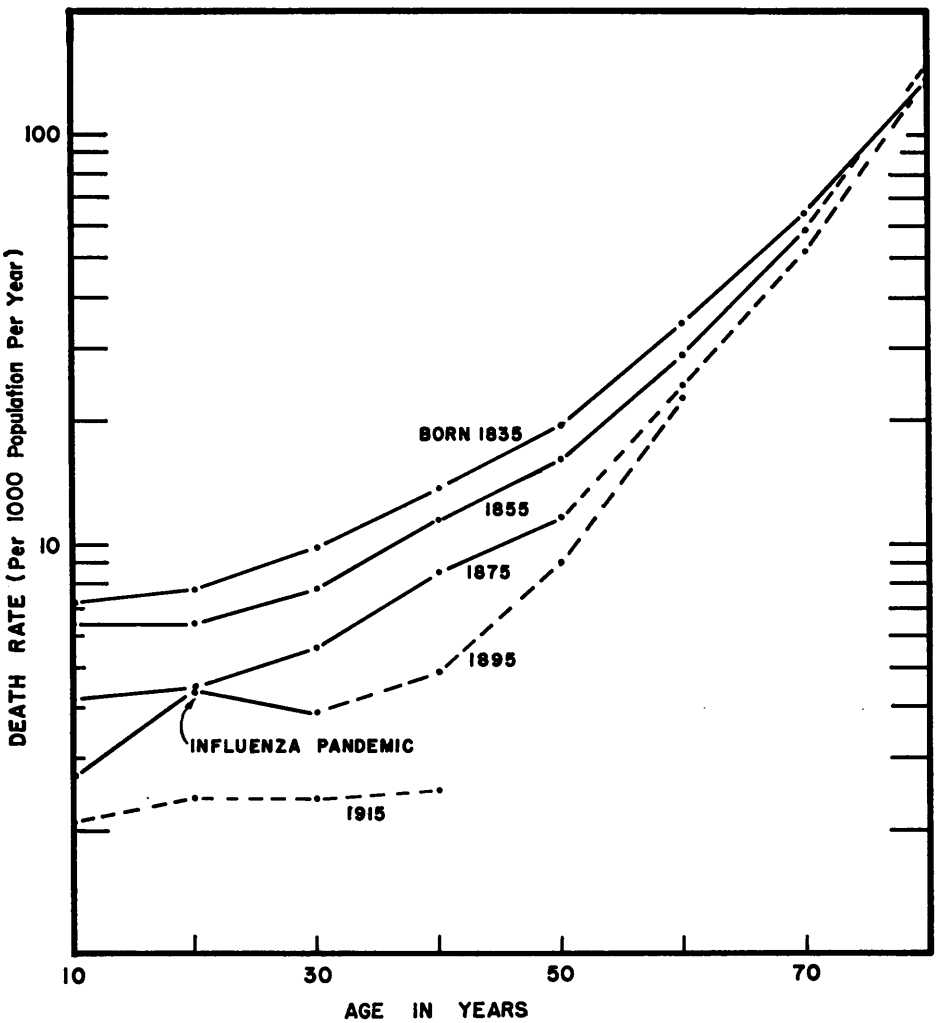

FIGURE 4

Cohort death rates by age: males, England and Wales, (see references [19], [43]).

Remember that Kermack, McKendrick, and McKinlay only had data up to 1930. On the basis of only those data there is an urge to assume that the populations really are becoming younger in the sense of the parallel downward displacement of the death rate curves. One might argue that a man 50 years old in 1945 was really, in terms of death rate, only as old as a 40 year old man in 1925. Naturally, we are most interested to learn if this difference is maintained into the older ages because, if so, this would correspond to an increase in life span, not just an increase in the expectation of life. When we bring in the 25

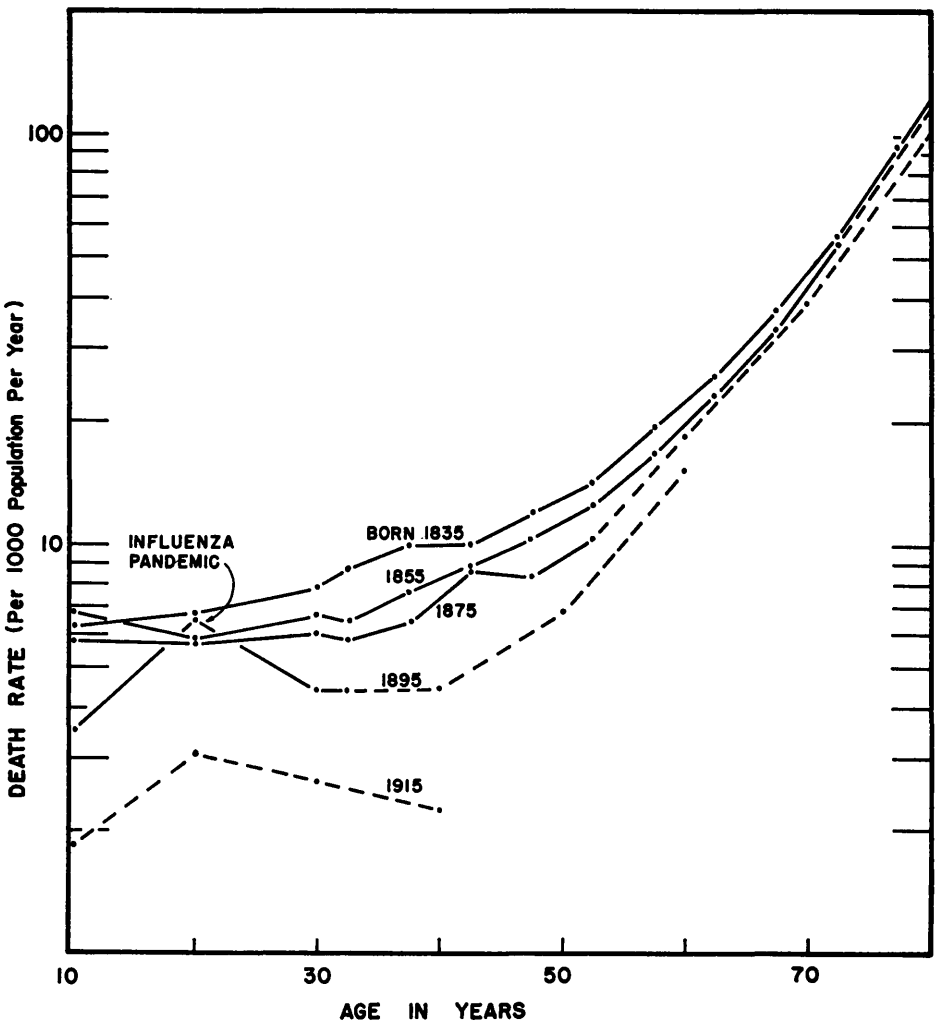

FIGURE 5

Cohort death rates by age: males, Sweden, (see references [7], [43]).

years of additional data which we now have, we find that the parallel displacement of mortality curves is not maintained into the old ages. There is a convergence of these curves with increasing age as shown in figure 4. When this same method of analysis is applied to Swedish data, the regularity seen in England and Wales does not appear, figure 5. For United States data there is some regularity but again the convergence of the cohort mortality curves seems apparent with increasing age, figure 6.

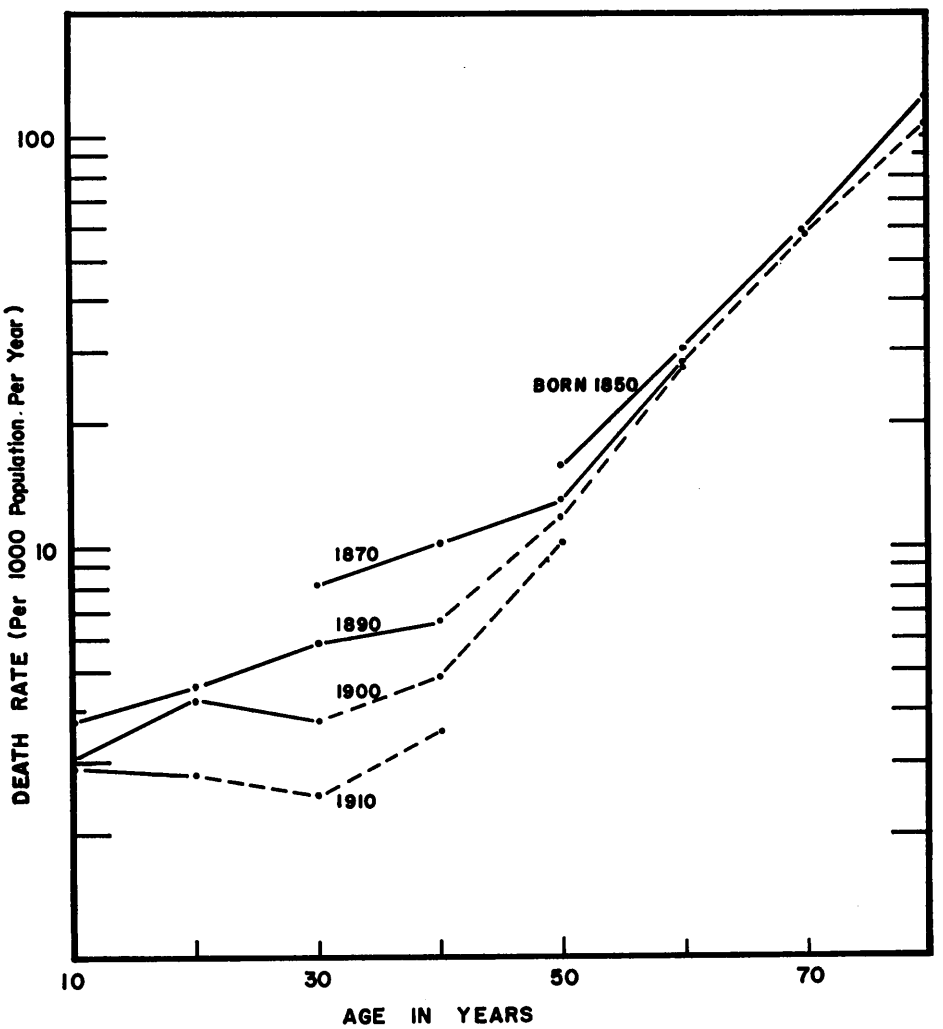

FIGURE 6

Cohort death rates by age: white males, United States,
(death registration states as of 1900)
(see references [30], [31]).

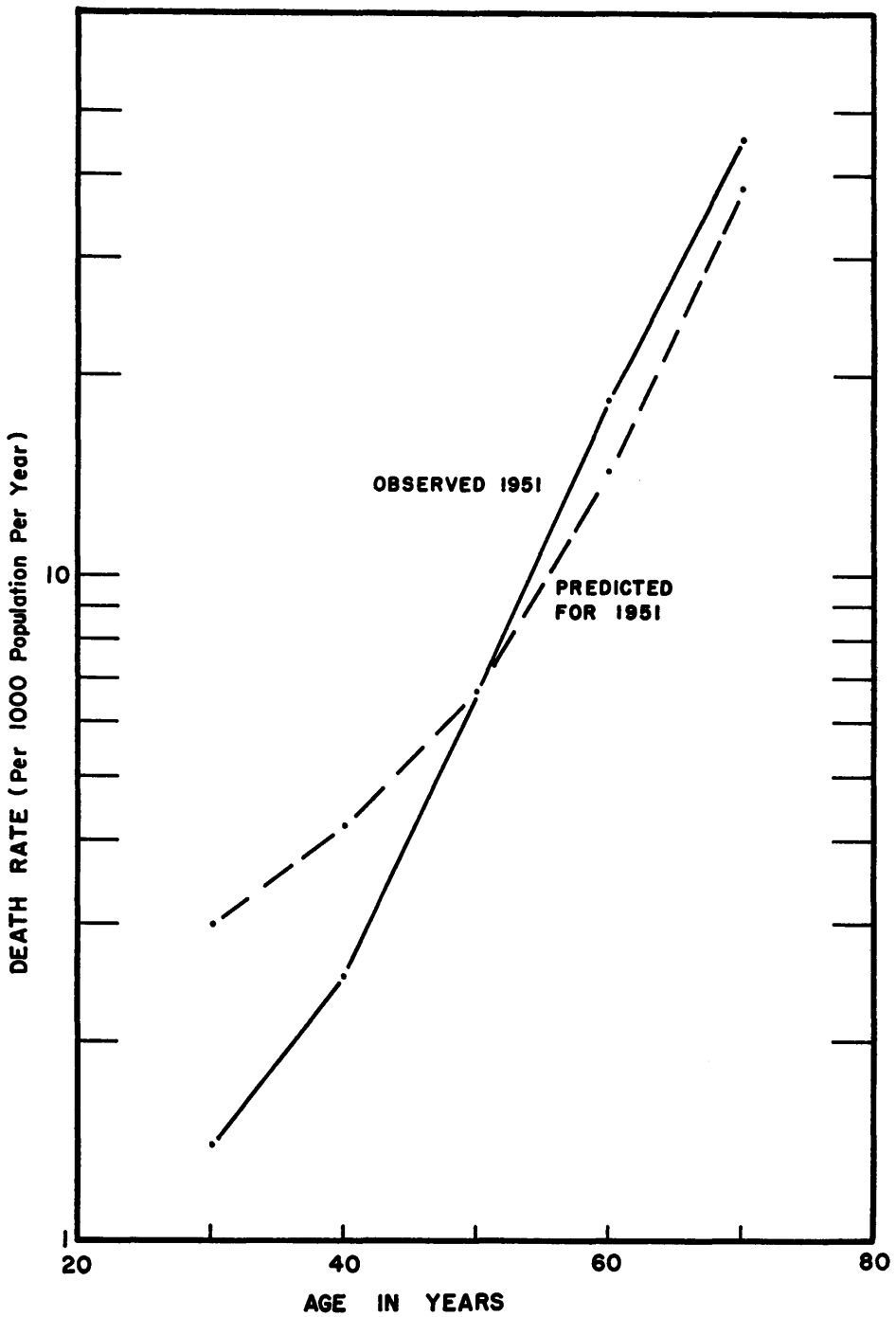

FIGURE 7

Death rates by age: both sexes, England and Wales, 1951, predicted by Kermack et al., 1934, and observed in 1951, (see references [19], [43]).

Observations such as those above immediately lead one to attempt to forecast death rates by extrapolating the observed constancies in the cohorts. By being here 25 years later, we can check the results of such a forecast as given by Kermack. We see that death rates at younger ages turned out to be lower than forecast with the reverse true at older ages. The proportionalism was not maintained into the higher ages. A spectacular decrease in mortality at ages under 50 was not anticipated. See figure 7.

The Kermack paper provides a simple mathematical model for the description of the progression of mortality rates. The model is a multiplicative one stating that the rate is equal to the product of a factor associated with the group or the cohort and a factor associated with age. When this model was fitted to recent data for the United States a systematic departure was found between the respective values as determined by the model and the observed values. The differences suggested that the model failed because it did not account for effects which were time related in addition to being cohort and age related.

A few years ago Sacher [37] used a linear model to describe the logarithm of the mortality rate. This model is a generalization of the Kermack one and was applied by Sacher to data on tuberculosis death rates. The model simply stated that the logarithm of the death rate is equal to the sum of a general effect δ plus an effect α_i for age, β_{j-i} for cohort, and γ_j for calendar time. The model is not particularly simple to fit to data by least squares because usually a sizable matrix must be inverted. However the matrix is fairly easy to write down and computer availability would make fitting the model a simple job. The trends with time and age of the parameters α_i, β_{j-i}, and γ_j would be of considerable interest.

Another model which was described only briefly in the paper by Cramér and Wold had to do with a generalized Makeham-Gompertz function to take into account variability in both age and calendar time. A statement was given by Cramér and Wold as to certain mathematical conditions implied by this model. No attempt to fit this model to data was published, however.

It should be obvious from the remarks above that the study of mortality data by cohorts is a useful adjunct to the more straightforward fixed-time analysis.

Jones [18] used the cohort analysis of Dorn [10] in relating the results of experimental findings on animals to human cancer. When animals are subjected to repeated low level irradiation, their mortality curves differ from those for control animals by being increased and at the same time rotated so that the slope of the curve is steeper. Jones, noting that lung cancer cohort mortality rate curves behaved in the same way, offered an explanation analogous to the chronic radiation experiment. There appeared a few years ago some carcinogenic substance which is cumulative. The effects of this accumulation are now seen as an increased slope of the mortality curve. Prior to Jones' work, Dorn [10] made similar conjectures but did not refer to the radiation results. This analysis is an intriguing one but it rests on rather shaky foundations in that we know so little, even about animals, with respect to survival following various stresses.

Faced with specific causes of death as an object of study we look for alternative methods for analyzing the data. The approach found very frequently in the literature is one of studying the age specific death rates for the particular cause in order to learn about trends with age and time. Jones [17] in addition to this, has constructed what he calls an abstract death rate. This is an attempt to build up artificially a population of people who are somehow particularly susceptible to the cause of death in question. The abstract death rate is defined as follows. Let D_{1x} be the observed deaths at age x from cause number 1 during some observation period of, say, one year. Let D_x be the total deaths during the year at that age, and P_x the population at age x as of midperiod. The abstract death rate J_{1x} is defined by Jones as

$$J_{1x} = \frac{D_{1x}}{\sum_{i=x}^{\infty} D_{1i}} \frac{\sum_{i=x}^{\infty} D_i}{P_x}. \tag{7}$$

When written as

$$J_{1x} = \frac{D_{1x}}{\sum_{i=x}^{\infty} D_{1i} \Big/ \sum_{i=x}^{\infty} D_i} \frac{1}{P_x}, \tag{8}$$

it is interpreted as the ratio of the number of deaths from cause number 1 at age x to the expected number of people who will eventually die from cause number 1 out of the people in the population at age x. This index can be interpreted in a variety of ways and has been used by Jones to compare specific disease populations with other groups with respect to the force of mortality. Jones, for instance, compares the abstract death rate for congenital malformations of the circulatory system with the total death rate for U.S. males, U.S. females, and other groups. In order to study the Jones index further, we rewrite it as

$$J_{1x} = \frac{D_x}{P_x} \frac{(D_{1x}/D_x)}{\left(\sum_{x}^{\infty} D_i \frac{D_{1i}}{D_i}\right) \Big/ \sum_{x}^{\infty} D_i} = m_x \frac{r_{1x}}{\sum_{x}^{\infty} w_i r_{1i}}. \tag{9}$$

The denominator is a weighted mean of the ratios D_{1i}/D_i, called r_{1i}, in which the weights w_i are all positive. Suppose that these ratios are increasing with age as is the case with the cardiovascular-renal diseases. Then J_{1x} must be less than the age specific total death rate m_x. If the ratios are decreasing, however, as in congenital malformations of the circulatory system, then J_{1x} must be greater than m_x. In the case of tuberculosis, J_{1x} at early ages is lower, at older ages higher than the corresponding age specific death rate. The comparison of the Jones index for different places and different times seems to be of questionable value. It certainly does not measure specific force of mortality associated with a cause of death, as implied by the comparisons made by Jones, for it is quite dependent on other causes of death which influence the ratios r_{1i} at later ages.

It seems to the author that there are no satisfactory substitutes for the age-

cause specific death rate in studying man's susceptibility to a cause of death. Of course, there are many measures of the impact of a particular cause on society. Life table functions, net probability of death from one cause in the absence of all other causes, changes in expectation of life by eliminating a cause of death—these are some of the indices in common use. Each has its use, but they depend on age specific death rates in their computation and none of them appears to offer as much for the study of the susceptibility of aging man as the simple age-cause specific death rate.

5.2. *Correlations among death rates.* Suppose we evaluate the association between death rates at age 10 in 1900 and those in the same place at age 60 in 1950. If we find positive association, we might say that similar environmental effects remained for 50 years influencing young and old alike; or we might say that high rates early in life lead to permanent damage reflected in high rates late in life. These two explanations are confounded here. If we find little or no correlation we are inclined to discount the effects of early environment or to wonder if there could be counteracting forces in some sense. Actually, when data for the United States are examined, we find no association between death rates from 5–14 and those from 35–44 in the cohort born between 1895 and 1905.

Mr. Leonard Marascuilo, a graduate student in biostatistics, carried out the above and several other correlation analyses, some of which were patterned after those done by Jones in 1956. Where Jones used his questionable "abstract death rate" Marascuilo used age-cause specific death rates. Let us assume that adverse environmental exposure early in life "conditions" a population so that its mortality by age is determined. For example, in comparing various countries having different environmental stresses suppose that we say some countries are "younger" than others in that their mortality curves are lower. If it is true that early high mortality rates prematurely age a population, we should find some consistency in this by observing an association in death rates by various causes at older ages. Marascuilo and also Jones [17] considered diseases of the cardiovascular system as opposed to all other causes of death. The former, however, studied the data in somewhat greater detail, breaking it down into separate age groups ranging from age 30 up to age 80. He computed rank correlation coefficients and found no consistency in the association in the age groups studied. The coefficients ranged from $+.56$ to $-.38$. The resulting impression was that there is no positive association between high cardiovascular disease death rates and all-other-cause rates.

The correlation method is a rather crude tool. Unfortunately it is also subject to giving spurious results. If, for example, in some countries there are rather poor medical diagnosis facilities, then there are apt to be reporting peculiarities on death certificates, particularly regarding just those systemic diseases in which we are interested. For instance, Marascuilo found a negative correlation between death rates from senility, which is an ill-defined, catch-all category, and death rates for malignant neoplasms. There was also a negative correlation between senility and arteriosclerotic heart disease. Such a situation could, in itself, lead

to a spurious correlation between malignant neoplasms and arteriosclerotic heart disease.

Other possibilities for spurious correlations exist. In the United States for deaths from each state during 1949–1951 (white males age 65–74), there apparently is a positive correlation between death rates from cardiovascular-renal disease on one hand and from malignant neoplasms on the other. Whether or or not this correlation is spurious is difficult to say. It is true that the quality of reporting varies from state to state, but probably not very much. The age group 65–74 is a ten year one and if certain states tended to have greater proportions of people in the upper range of this interval then there is a possibility for some sort of spurious relationship. Marascuilo found a positive association between malignant neoplasms and per cent of population age 65–74. There was also a positive association between diseases of the heart and per cent of the population age 65–74. He reasoned that states having greater percentages of population in the age group 65–74 would be those states which have a greater proportion of people at the higher end of the age group 65–74. The possibility of spurious correlation exists, therefore, but the matter has not yet been studied carefully enough to be reasonably sure of the situation. It appears that the impressions obtained from correlation studies on death rates are difficult to evaluate and should be treated with critical care.

5.3. *Methods based on differences in stress exposure early in life.* Studies based on groups having had different early life exposure are perhaps those approaching most closely the ideal experimental procedures which are necessary for definitive findings. *The guiding principle here is to study groups of people all of whom are subjected to roughly the same environment in their adult life but who underwent different stress circumstances in their youth.*

An example of this method is found in the statistics collected in the United States concerning death rates of the foreign born. The age specific death rates among foreign born can be compared reasonably with the rates for native born if proper care is taken to keep the comparison free from extraneous variables, such as urban versus rural living, occupation, geographic location, and so forth. Immediate objections to any study of immigrants compared with natives can be raised because people who have the energy to migrate from their own country to the United States are apt to be somewhat selected and might be expected to be a hardy group of people. Ignoring this difficulty we study what is available. Thirty years ago a sizable proportion of the population of the United States was foreign born. Many interesting studies were made [13]. It was found, for instance, that the death rates for the foreign born were considerably higher than the comparable ones for native born people. The difference tended to disappear at the older ages and practically entirely disappeared by 1940 when the publishing of these data was stopped. The proportion of foreign born now is rather small in the United States. However, in some countries such as New Zealand, Australia, and Canada a sizable amount of immigration has occurred in the very recent past and studies of this sort would seem to be reasonable ones to pursue. There

have been some scattered reports concerning immigrants to New Zealand and Australia from the United Kingdom with respect to their susceptibility to lung cancer [11]. Of use in this sort of study is the fact that during World War II millions of people lived in substandard conditions with respect to housing and nutrition. Many of these people have since migrated to countries which were not so destitute during the war. Thus there exists a suitable study group to be compared with the native populations in the adopted countries.

This same method could be applied to other situations. Persons accepted by military organizations can be categorized with respect to their place of birth, and hence roughly labeled in accordance with the health conditions of their early life. While in the military, they are subjected to quite uniform living conditions and medical care. Fairly complete health records are available, including a medical history. The drawback, of course, is the short length of time such people are usually retained by the military under these uniform conditions. Physical and mental misfits, also, are quickly discarded by the military organizations. A favorable point is that, through the activities of the selective service system, samples of United States young men are obtained which are at least free from the self-selective aspect that occurs in volunteer enlistment.

In connection with using the military system for research on aging, a rather large number of career officers and enlisted men for whom medical and service records exist for nearly 20 years could be studied with respect to indices of early environment, medical history, and subsequent survival. A strong point in favor of the use of military sources, in spite of the nonrepresentativeness of its members, is the existence of records documenting their health and careers. Also career soldiers receive military medical care after retirement, an important consideration.

A source of information which has great promise is the new state of Israel with its many thousands of people with a wide variety of early environmental experience. Active observation is now going on and a few publications have appeared [35]. Israel is analogous to many other countries, such as those mentioned above, which have received immigrants. The difference lies in the very large numbers received by Israel, the exceedingly wide variety of previous environment, and the highly developed and easily available medical service for its population.

An active program is being carried out by the National Research Council utilizing Veterans Administration data. Men who were subjected to various severe experiences while in the armed forces are available for follow-up study and can be contrasted to control groups of men with less stressful experience. While these stresses occurred in early adulthood and therefore may not have occurred during the most impressionable period, they still form a basis for questions related to the subject of early environment and subsequent later susceptibility to death. A number of studies have already been published including one concerning prisoner of war populations and their susceptibilities to death following apparent recovery from their wartime exposure [5].

We must not ignore the extensive work done by insurance statisticians in their many studies of physical impairments and survival [20], [24]. While there are objections to the selection of subjects, choice and determination of impairments, and so forth [20] the findings are of great value within their limitations. They point out the higher subsequent death rates for people who have at the time of issuance of insurance conditions such as obesity, high blood pressure, heart murmurs, gastric ulcers, and the like. Apparently they have not studied people in accordance with early environment, acute communicable disease experience (except tuberculosis which is closely studied), education, or physical activity.

Work of unusual interest was published by Madigan and Vance [21], [22]. They achieved the closest approximation yet found to the ideal experimental situation needed for sound results. They obtained the longevity records for a number of communities of Catholic teaching Brothers and Sisters. Their purpose was a comparison of mortality among men and women who led equivalent lives. The situation, however, is amenable to studying longevity with respect to the conditions of life experienced by these Brothers and Sisters during their formative years prior to their entering their organizations. The main weakness here is the possible (probable?) lack of information on health experience during those years of childhood.

There are many possibilities for exploitation of certain types of records when these records are coupled with the newly developed matching procedures of the high speed computers. For example, school health records exist which provide an index of the illness experiences of many thousands of children. This gives a starting point for a large-scale operation to match names obtained from school records with death certificates in later years. This is undoubtedly premature at this time but it is rapidly becoming possible.

5.4. *Occupational statistics and mortality.* As is only natural, considerable effort has gone into the study of occupational mortality. By far the best information on this is collected in England [36], [40], and there are available extensive and detailed tabulations, particularly for the years 1930–32 and 1950–52. Mortality by detailed occupation, geographic location, age, cause of death, and social class are tabulated. The mortality of women is studied by the occupation of the husband, thus providing a kind of measure of mode of living under the assumption that the wife is not exposed to the industrial hazards which the husband faces. Nearly all writers on this subject express an awareness of the difficulties regarding the believability of the findings [4], [9], [27]. Trouble stems partly from the fact that census information provides the data on occupation giving the populations at risk in various occupational groups. We in this country have just gone through a census and can recognize the inherent error in recording occupational data, particularly when one remembers that the data are usually obtained from the housewife but are frequently obtained from a neighbor. Ignoring this source of error, however, there is the embarrassing fact that the occupation for those people who die is obtained not from the census but from death certificate. In most states of the United States, for example, census occupation is

"current" occupation and death certificate occupation is "usual" occupation. A few years ago, the State of California changed its death certificate to agree more closely with the census occupation question. Because we do not know the relationship between occupation data provided by the census and provided by the death certificate, it is difficult to evaluate sensibly the occupational mortality results. It is most gratifying to know that soon there will be an extensive study made in this country of the agreement between the census reports and death certificates. This will aid considerably in the evaluation of such mortality data. A possibility which does not seem to have been explored very much is that of referring each death back to the census report for the occupation of the deceased. On the face of it, this sounds like an impossible task, but as mentioned previously in the light of recent work [33], on the use of high speed computers in matching large numbers or records, such a procedure seems worthy of pursuit.

Turning from the criticism of the method of occupational mortality, we examine some of the recent results [3], [42] obtained by studying mortality when occupations are grouped into five standard groups called social classes. These social classes range from the lowest class of manual unskilled workers to the highest class consisting of professional people, clergymen, and so forth. Total mortality, when considered age by age, seemed to vary inversely with social class; the higher the social class, the lower the mortality. When deaths were divided into two groups, one consisting of causes such as cancer, diabetes, heart disease, hypertension, and nephritis, generally the so-called endogenous diseases, this trend with social class was reversed at older ages. The highest social class has the highest endogenous death rate. With respect to all other causes, that is, the so-called exogenous causes of death, again the death rate was highest among the lowest social classes at all ages. This is a very interesting point which has been brought out in several papers during the past twenty or thirty years. The protection accorded to the highest social classes from exogenous causes of death exerts a kind of adverse selectivity leaving these classes weaker at the older ages than the survivors among the lower social classes. Analogous findings are observed with respect to the white and nonwhite death rates by age in the United States. Nonwhite male death rates are much higher than white ones at the earlier ages but become lower than white death rates at the older ages. See figure 1. In both of these examples, peculiarities in the data exist and believing in the results is dependent upon special scrutiny of the data.

6. Discussion

A few things which are noteworthy by their intractable nature or by the inattention received by them in the literature will be mentioned here as the concluding part of this paper. These are not given as though they were new ideas; they simply do not seem to have received as much attention as they deserve.

6.1. *Exercise.* There does not seem to be much known about exercise and longevity [16], [26]. Of course occupations have been categorized in terms of

physical activity, and a few studies [28], [29] have been made of such occupational groups as streetcar motormen (inactive) and conductors (active). The problem of self-selection is present here to such an extent that belief in results is very difficult. Strangely enough even animal experimentation on exercise seems rare. Suggestion: Obtain information on the exercise taken by men all of the same occupation, such as physicians. This will require special surveys but might be tied in with the National Health Survey. The information would be stored for future matching against death certificates.

6.2. *Education.* Educational level or academic achievement should be tied in with occupational status and mortality. There are indications [26] that college graduates have about two years greater expectation of life than the general population. Among college graduates, honor students seem to have the greatest expectation of life. College athletes are reported to have a life expectancy very close to that of the general college graduate.

6.3. *Migration.* What becomes of the rural young people who finish school and move to the city, as compared with the city-reared person? Data are hard to obtain in this field. Even if census data on migration could be used, the problem of matching to death certificates remains.

6.4. *Self-selection.* While we can probably do little about the initial selection of occupation or habits or environment, we might be able to change something about these things at random. This changing of conditions could, for example, apply to a group of smokers (who are, of course, self-selected), half of whom are put under pressure to stop smoking and half of whom are not influenced. This might be used in studying low income people, some of whom go into special housing while the remainder stay in crowded slums. It could also be used in studying public health sanitation services which are randomly located in part of an area of poor environment.

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